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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,162	02/08/2000	Judes Poirier	08523/006002	2201

21559 7590 11/02/2004

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/500,162	POIRIER, JUDES	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-8 and 10-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-8 and 10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08162004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' submission filed on 16 August, 2004, has been entered.

Status of the Claims

Claims 1, 3, 5-8, and 10-14 are currently under examination.

Information Disclosure Statement

The information disclosure statement filed 16 August, 2004, has been placed in the application file and the information referred to therein has been considered as indicated. Applicants are advised that a copy of the Landen *et al.* (1996) publication did not accompany the PTO-1449.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-8, and 10-14 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. As previously set forth the claimed invention is broadly directed toward the use of *apo*E allele determinations to predict the clinical efficacy of a given drug in patients with various neuropathologies. The disclosure describes a method for creating a prognostic protocol for late onset Alzheimer's disease (AD) patients by examining ApoE protein levels. It was reported that individuals carrying one or both copies of the ε4 allele display a poorer clinical outcome as compared to those late onset AD patients lacking the allele. Thus, the claimed invention is enabled only as it applies to late onset AD patients. Applicants were advised that appropriately drafted claim language directed toward this embodiment would be acceptable. However, the disclosure is not enabling for claim language directed toward any and all other neurological diseases.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The claims are excessively broad and encompass an extremely large genus of disparate neurological disorders. The claims are directed

toward Alzheimer's disease (AD), neurofibromatosis (NF), Huntington's disease, depression, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, multiple infarcts dementia, prion disorders (e.g., Creutzfeldt-Jakob disease), pathologies of the developing nervous system (e.g., arginosuccinic aciduria, cystathionuria, histidinaemia, homocystinuria, hyperammonaemia, phenylketonuria, fragile X syndrome), pathologies of the aging nervous system, infections, dietary deficiencies, and cardiovascular injuries. However, these sundry disorders all have different pathological determinants (Martin and Longo, 1998; Timchenko *et al.*, 1996; Salvatore *et al.*, 1995; Brouillet *et al.*, 1995). The molecular determinants modulating many of these disorders have been mapped to chromosomal regions unrelated to those of late onset Alzheimer's disease (see Table 363-1, pp. 2294-2303). Moreover, for those neurological disorders with a clear mechanism of disease, most of them do not involve the Apolipoprotein E4. For instance, Creutzfeldt-Jakob disease is caused by a prion protein, Wilson's disease is caused by a defective membrane ATP-ase, amyotrophic lateral sclerosis is caused by a mutant superoxide dismutase (*SOD*1), other forms of amyotrophic lateral sclerosis have been attributed to a mutant neurofilament heavy chain protein, and fragile X syndrome is caused by trinucleotide repeats in the 5' region of the *FMR*-1 géne. Thus, many of these disorders fail to share any genetic linkages or biochemical mechanisms with those of late onset AD and *apo*E allele frequency. Accordingly, the skilled artisan would not consider it reasonable to assert that the *apo*E allele frequency in all these various disorders, many of which do not directly involve Apo E-regulated transport and internalization of cholesterol and phospholipids, would be predictive of therapeutic responsiveness and clinical outcome. Furthermore, even if the underlying mechanism did affect lipid metabolism, it does not mean that changes in the *apo*E allele load are responsible for the defect. The defect could be

present in a downstream or upstream step of the pathway independent of the presence or absence of any given *apo* E allele. The disclosure clearly fails to provide sufficient guidance pertaining to this concern.

2) The disclosure fails to establish any correlation between *apo*E ε4 allele loads and any given neurological disorder other than late-onset AD. As noted in the preceding paragraph, the molecular basis for many non-AD neurological disorders remains to be elucidated. For those disorders that have been characterized, most of them do not involve disorders of ApoE-regulated transport and internalization of cholesterol and phospholipids (Martin and Longo, 1998). Thus, the disclosure fails to provide any guidance pertaining to the specificity, sensitivity, and predictive value of measuring the *apo* E allele frequency in any of these disorders.

3) The disclosure fails to provide adequate guidance pertaining to the predictive value of measuring *apo*E allele loads with any particular class of therapeutics. In AD, the *apo*E ε4 allele load is reasonably predictive of patient responsiveness to cholinomimetic therapy. This is not surprising considering the finding that late-onset AD patients have decreased levels of choline and decreased ChAT activity. However, the disclosure fails to provide any guidance pertaining to other suitable therapeutic compounds and the predictive value of measuring the *apo*E allele load in these settings.

4) The disclosure fails to provide any working embodiments involving non-AD neurological disorders. The only example provided involves the relationship between *apo*E allele frequency and cholinomimetic responsiveness in late-onset AD patients. Examples involving non-AD neurological disorders were not provided.

5) The prior art clearly teaches that *apo* E allele frequencies do not correlate with most non-AD neurological disorders. For example, Morris *et al.* (1996) state(abstract, p. 205) that "We have genotyped a

large series of clinically and neuropathologically confirmed cases of AD ... No changes in APO E allele frequencies were found in presenile AD, Parkinson's disease with or without dementia, or in Down's syndrome." The authors further reported (abstract, p.205) that "Whilst there appears to be a strong association between the APO E allele and AD and also in LBD, other related neurodegenerative disorders associated with dementia do not show such a linkage." The authors were unable to demonstrate any apparent association between APO E ε4 levels and vascular dementia, Parkinson's disease, alcoholic dementia, and Down's syndrome (p. 207, bottom paragraph). The authors further summarized their studies and reported (p. 212, first full paragraph) that "Recent studies (Saunders et al., 1993; Pickering-Brown et al., 994; Royston et al., 1994; Martins et al., 1995; Wisniewski et al., 1995) have failed to show an increased ε4 frequency in Down's syndrome patients, and the present results would appear to confirm this" and that (p. 212, second paragraph) "Both demented and non-demented Parkinisonian patients showed no significant increase in APO E ε4 frequence, compared to age-matched controls, suggesting that the biological basis of dementia in PD differs from that found in AD and LBD and is not linked to APO E (Benjamin et al., 1994; Koller *et al.*, 1995; Marder *et al.*, 1994)." Additional studies by Mattila *et al.* (1998) confirmed these findings. The authors reported (abstract, p. 417) that "The results show that neuropathologically verified PD as such is not associated with increased apoε4 allele frequency." It was further noted (p. 419, first paragraph, Discussion) that "our results confirm the findings of clinical series [3, 11, 14] showing no increase in apoε4 allele frequency in PD. The results of most of the previous neuropathological series of PD [4, 9, 26] were also similar to those in our study." Earlier work by Rubinsztein *et al.* (1994) was also consistent with these findings. The authors noted (p. 519, abstract

and p.523, rt. col.) that "No significant alteration in the apo E allele distributions was observed in any of these conditions [i.e., multiple sclerosis, Parkinson's diseases, sporadic vestibular schwannomas, and neurofibromatosis], nor did the apo E genotypes correlate with disease severity" and "No significant associations were detected with any of the apo E alleles or genotypes with multiple sclerosis or Parkinson's disease. In addition, no relationship was detected between the onset of Parkinson's disease and any apo E genotype. It is thus unlikely that apo E plays an important role in the pathogenesis of these diseases." Salvatore *et al.* (1995) also reported (refer to Abstract, page 95) that "Our results provide further evidence that ApoE is not a risk factor for CJD." Finally, Marder *et al.* (1994) also observed (p. 1330, abstract) that "There was no association between Apoε4 and dementia in the PD patients. We conclude that the biologic basis for dementia in PD may differ from that of AD." Thus, the prior art clearly illustrates that the *apo*E ε4 allele is not responsible for many neurological deficits. Therefore, determining the *apo*E allele load would be of no predictive value.

Additional studies by Weatherby *et al.* (2000) reported (p. 532, concluding paragraph) that "The results of this investigation in patients with primary progressive disease suggest that the ε4 allele does not influence prognosis in this group. When considered together with our findings in a large cohort of 370 patients with relapsing-remitting and secondary progressive disease which also showed no evidence of an association between allelic variation of APOE and disability, we suggest it is unlikely that the ε4 allele when considered alone significantly influences prognosis in multiple sclerosis." Finally, Whitehead *et al.* (1996) reported (p. 347, abstract) that "The results from our study as well as the pooled meta-analysis exclude any important role for ApoE ε4 status in the development of Parkinson's disease. Our results similarly do not

support its role either in dementia associated with Parkinson's disease or disease prognosis." Thus, the prior art fails to provide any meaningful correlation between ApoE allele load and several neurological disorders including neurofribomatosis, multiple sclerosis, Parkinson's disease (PD), and prion disorders. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention in a manner commensurate in scope with the claims. Applicants arguments have been carefully considered but are not deemed to be persuasive. Applicants continue to argue that the specification and previous declaration of Dr. Poirier enables the full breadth of the claimed invention. This position is clearly untenable given the large number of publications that provide data that clearly demonstrates that ApoE allele load does not play a role in several neurological disorders.

Non-statutory Double Patenting

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman*, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a

registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

Claims 1, 3, 5-8, and 10-14 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,935,781. Although the conflicting claims are not identical, they are not patentably distinct from each other. As previously set forth, the claims of the instant application are directed toward prognostic protocol methods involving patients with neurological disorders and *apo*E allele load determinations while the claims of the '781 patent are directed toward patient prognostic protocols involving patients with cognitive impairments, which are caused by CNS pathologies. Thus, the claims of the '781 patent fall within the scope of the claimed invention and would result in the unjustified or improper timewise extension of the "right to exclude" granted by a patent. Applicants stated that a terminal disclaimer would be filed when allowable subject matter has been identified.

The previous provisional rejection of claims 1, 3, 5-8, and 10-14 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 09/865,753, is hereby withdrawn in response to the abandoned status of the application.

No claims are allowed.

Interview Request

Acknowledgement is hereby made of the request for an interview. Applicants are invited to contact the Examiner to arrange a mutually convenient time and date.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, James C. Housel, can be reached at (571) 272-0902, respectively. Direct general inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

29 October, 2004